REMARKS/ARGUMENTS

Objection to Specification

The disclosure is objected by the Examiner because adding an incorporation-by-reference statement in a benefit claim is not permitted after filing.

The specification is amended to delete the incorporation-by-reference statement in the benefit claim. Therefore, Applicants respectfully request the Examiner withdraw the objection to the disclosure.

35 U.S.C. §112 First Paragraph Rejection

Rejection to Claims 36-37

Claims 36-37 are rejected under 35 U.S.C. §112, first paragraph because the specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. Applicants respectfully traverse this rejection in light of the following comments.

The hybridoma which produces the monoclonal antibody designated M195 has been deposited with the American Type Culture Collection in Rockville, Md., U.S.A. 20852 (address has changed to PO Box 1549, Manassas, VA 20108), under ATCC Accession No. HB-10306 on Dec. 14, 1989. This deposit was made pursuant to the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure (Budapest Treaty). (See U.S. Patent No. 5,730,982, col. 5, lines 41-48). An excerpt from the ATTC website showing that the antibody can be ordered from the ATTC for a fee of $290 is attached. Should the Examiner still not be satisfied regarding public availability, applicants invoke 37 CFR 1.808(c). Applicants request the Examiner or other appropriate person within the PTO to whom the Examiner might refer this matter certify that ATCC HB-10306 is publicly available. A separate request for certification is attached.

In light of the publicly available hybridoma HB-10306 from ATCC, Applicants respectfully request that the Examiner withdraw the rejection of claims 36-37 under 35 U.S.C. §112, first paragraph.

Rejection to Claims 30-45

Claims 30-45 are rejected under 35 U.S.C. §112, first paragraph, on the grounds that "the specification, while being enabling for a mutant antibody that comprises an amino acid substitution that eliminates a variable region framework glycosylation site of the parent wherein said elimination has the effect of increasing the affinity of the mutant relative to the parent, does not reasonably provide enablement for a mutant antibody that comprises an amino acid substitution that eliminates a variable region CDR glycosylation site of the parent wherein said elimination has the effect of increasing the affinity of the mutant relative to the parent (page 5, line 5 of the Office Action)." The gist of the position taken by the Examiner appears to be that "the specification does not demonstrate which residues to substitute or which residues when substituted would likely result in higher affinity as required in the claims. The Examiner profers that it would be undue experimentation to identify which residues to substitute in order to generate an antibody that results in increased affinity (page 6, line 13 of the Office Action)." The rejection is respectfully traversed.

The specification provides ample guidance for making the claimed antibodies. The specification teaches that "when the parent immunoglobulin sequence contains a glycosylation site in a V region framework, particularly in a location near the antigen binding site (for example, near a CDR), the glycosylation site sequence is mutated (e.g., by site-directed mutagenesis) to abolish the glycosylation site sequence, typically by producing a conservative amino acid substitution of one or more of the amino acid residues comprising the glycosylation site sequence (page 12, line 30 to page 13, line 7). The specification teaches that when the parent immunoglobulin sequence contains a glycosylation site in a CDR, and the parent immunoglobulin specifically binds an epitope that contains carbohydrate, that glycosylation site is preferably retained. If the parent immunoglobulin specifically binds an epitope that comprises

only polypeptide, glycosylation sites occurring in a CDR are preferably eliminated by mutation (e.g., site-directed mutation)." The specification further teaches that "a limited number of amino acids in the framework or CDRs of a humanized immunoglobulin chain are chosen to be mutated (e.g., by substitution, deletion, or addition of residues) in order to increase the affinity of an antibody" (page 15, line 21).

Identifying which residues to substitute to result in an antibody with an increased affinity does not require undue experimentation. Sox and Hood, Proc. Natl. Acad. Sci. USA 66:975 (1970) reported that only about 20% of human antibodies are glycosylated in the V region. (See page 2, lines 2-4 of the specification). In antibodies that are glycosylated in the V region, the glycosylation site can be readily identified (see page 6, line 36 to page 7, line 30 of the specification). Although there are about 60 amino acids in the CDRs of an antibody, only a few of these could possibly be a glycosylation site. That is because N-linked carbohydrate groups can only be linked to Asn in the sequence Asn-X-Ser/Thr, and O-linked carbohydrate groups can only be linked to Ser or Thr, predominantly in the sequnce Ser/Thr-X-X-Pro (see page 7, lines 5-13 of the specification). Moreover, changing the Asn or respectively the Ser/Thr in these sequences to any other amino acid always eliminates the glycosylation site. Hence, to test whether elimination of a glycosylation site in the CDRs increases affinity, it is at most necessary to make a single mutation at each of a few amino acids, which was well within routine experimentation at the priority date of the application. Of course, eliminating a glycosylation site in the CDRs (or framework) will not always increase the affinity. Such cases in which eliminating the glycosylation site does not increase affinity would not fall within the scope of the present claims.

Once a putative glycosylation site is identified, one of ordinary skill in the art, following the routine molecular biology techniques (see page 16, lines 8-17 of the specification) is able to make a mutant construct to eliminate such glycosylation site, produce the mutant antibody and measure its affinity. The teachings in the specification have been followed by one of ordinary skill in the art to make a claimed antibody as demonstrated in WO 03/016466 A2. In the background, the '466 publication acknowledges the inventors of the present application (i.e., Co

et al.) for the discovery that glycosylation sites can lower antibody affinity (see p. 3, liens 7-10). In Example 6 (at p. 37), a glycosylation site was recognized in the CDR2 of the heavy chain and only two mutants were engineered to eliminate the glycosylation site. Both mutants were shown to have an increase in binding affinities of about 6 fold when compared to the original humanized antibody. This example shows that identifying which residues to substitute to result in increased affinity does not require undue experimentation.

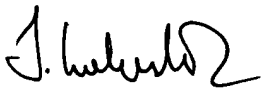
The Federal Circuit considered the issue enablement posed by screening antibodies for affinity in *In re Wands*. The issue in *Wands* was whether the specification of the *Wands* patent enabled production of a class of antibodies having IgM isotype and a binding affinity of at least 10^9 M^{-1} using Kohler Milstein technology. As the Examiner is aware, Kohler Milstein technology is a classical technique that involves individualized screening of hybridomas to identify a subset with desired binding characteristics. Until the hybridomas have been screened, it is unpredictable which will have the desired characteristics. The evidence indicated that only a small percentage of the hybridomas to be screened would produce antibodies having the desired property. Nevertheless, the court found that "practitioners of this art are prepared *to screen negative hybridomas in order to find one that makes the desired antibody*" (858 F.2d at 740, emphasis supplied). The *Wands* patent was held to be enabled.

As outlined above , there is no difficulty producing the mutant antibodies of the presently claimed invention following the teaching of the specification. The experimentation required to identify variable region glycosylation sites that may be mutated to produce an antibody with increased affinity relative to the parent antibody is routine, and the specification provides guidance with respect to the direction the experimentation should take. Neither an extended period nor a considerable amount of experimentation is required to determine which sites can be successfully mutated. Moreover, even if it is assumed arguendo extended or extensive experimentation were required, it would not be undue because the methods used are routine and the specification provides guidance with respect to the direction the experimentation should take. Moreover, as was found in the Wands case, it is routine in the antibody technology art to carry out screening in determining which antibody has an increased affinity. The successful example

provided in the above cited patent application fully supports Applicants' position. For these reasons, Applicants request the rejection of claim 30-45 under §112, first paragraph be withdrawn. ATTC HB-10306 Cell Lines Information is attached as Attachment A.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



Joe Liebeschuetz
Reg. No. 37,505

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 650-326-2400
Fax: 415-576-0300
Attachments
JOL/drm
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Cell Lines

ATCC Number:	**HB-10306** Order this item	**Price:**	**$290.00**
Designation:	M195	**Depositors:**	Sloan-Kettering Institute for Cancer Research
Biosafety Level:	1 **Shipped:** frozen	**Isotype:**	IgG2a
Medium & Serum:	See Propagation	**Growth Properties:**	suspension
Organism:	*Mus musculus* (B cell); *Mus musculus* (myeloma) (mouse (B cell); mouse (myeloma))	**Morphology:**	lymphoblast
Tissue:	B lymphocyte; hybridoma		
Cellular Products:	immunoglobulin; monoclonal antibody; against human myeloid leukemia (CD33)		

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Related Cell Culture Products

Comments:	Animals were immunized with leukemia cells from a patient with acute non-lymphoid leukemia (ANLL). Spleen cells were fused with Sp2/0-Ag14 myeloma cells. The antibody detects an antigen found on early myeloid cells, monocytes, and ANLL cells but not on cells of other hematopoietic or nonhematopoietic lineages. [47016] It is reactive with CD33, a glycoprotein found on myeloid leukemia blasts and early hematopoietic progenitor cells but not on normal stem cells. [47024]
Tumorigenic:	doubly pristane-primed (C57BL/6 X BALB/c)F1 mice.

Propagation:	**ATCC complete growth medium:** RPMI 1640 medium with 2 mM L-glutamine adjusted to contain 1.5 g/L sodium bicarbonate, 4.5 g/L glucose, 10 mM HEPES, and 1.0 mM sodium pyruvate, 90%; fetal bovine serum, 10% **Temperature:** 37.0 C
Subculturing:	Cultures can be maintained by the addition of fresh medium or replacement of medium. Alternatively, cultures can be established by centrifugation with subsequent resuspension at 1 to 2 X 10 exp5 viable cells/ml. Maintain cell density between 1 X 10 exp5 and 1 X 10 exp6 viable cells/ml.
Freeze Medium:	culture medium 95%; DMSO, 5%
Related Products:	Recommended medium (without the additional supplements or serum described under ATCC Medium) - ATCC 30-2001 recommended serum - ATCC 30-2020
References:	47016: Scheinberg DA . Therapeutic use of hypervariable region of monoclonal antibody M195 and constructs thereof. US Patent 5,730,982 dated Mar 24 1998 47022: Tanimoto M , et al. Restricted expression of an early myeloid and monocytic cell surface antigen defined by monoclonal antibody M195. Leukemia 3: 339-348, 1989. PubMed: 2716349 47023: Scheinberg DA , et al. Monoclonal antibody M195: a diagnostic marker for acute myelogenous leukemia. Leukemia 3: 440-445, 1989. PubMed: 2725060 47024: Scheinberg DA , et al. A phase I trial of monoclonal antibody M195 in acute myelogenous leukemia: specific bone marrow targeting and internalization of radionuclide. J. Clin. Oncol. 9: 478-490, 1991. PubMed: 1999719

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